

# Intrauterine Exposure to Paracetamol and Aniline Impairs Female Reproductive Development by Reducing Follicle Reserves and Fertility - DTU Orbit (08/11/2017)

## Intrauterine Exposure to Paracetamol and Aniline Impairs Female Reproductive Development by Reducing Follicle Reserves and Fertility

Studies report that fetal exposure to paracetamol/acetaminophen by maternal consumption can interfere with male reproductive development. Moreover, recent biomonitoring data report widespread presence of paracetamol in German and Danish populations, suggesting exposure via secondary (nonpharmaceutical) sources, such as metabolic conversion from the ubiquitous industrial compound aniline. In this study, we investigated the extent to which paracetamol and aniline can interfere with female reproductive development. Intrauterine exposure to paracetamol by gavage of pregnant dams resulted in shortening of the anogenital distance in adult offspring, suggesting that fetal hormone signaling had been disturbed. Female offspring of paracetamol-exposed mothers had ovaries with diminished follicle reserve and reduced fertility. Fetal gonads of exposed animals had also reduced gonocyte numbers, suggesting that the reduced follicle count in adults could be due to early disruption of germ cell development. However, ex vivo cultures of ovaries from 12.5 days post coitum fetuses showed no decrease in proliferation or expression following exposure to paracetamol. This suggests that the effect of paracetamol occurs prior to this developmental stage. Accordingly, using embryonic stem cells as a proxy for primordial germ cells we show that paracetamol is an inhibitor of cellular proliferation, but without cytotoxic effects. Collectively, our data show that intrauterine exposure to paracetamol at levels commonly observed in pregnant women, as well as its precursor aniline, may block primordial germ cell proliferation, ultimately leading to reduced follicle reserves and compromised reproductive capacity later in life.

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Authors: Holm, J. B. (Ekstern), Mazaud-Guittot, S. (Ekstern), Danneskiold-Samsøe, N. B. (Ekstern), Chalmey, C. (Ekstern), Jensen, B. (Ekstern), Nørregård, M. M. (Ekstern), Hansen, C. H. (Ekstern), Styrihave, B. (Ekstern), Svingen, T. (Intern), Vinggaard, A. M. (Intern), Koch, H. M. (Ekstern), Bowles, J. (Ekstern), Koopman, P. (Ekstern), Jåégou, B. (Ekstern), Kristiansen, K. (Ekstern), Kristensen, D. M. (Ekstern)

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